ANNEX D

DRAFT TALK TO EPA SAB

Introduction

I am happy to have the chance to talk today. The possible effects of passive smoking on health have been a particular interest of mine for over a decade and my work is cited by the EPA in numerous places. Before commenting on specific aspects of the draft report I would like to make a number of points clear.

Firstly, although my passage is paid by the tobacco industry, I am here today because I wanted to be here and the views I express are my own.

Secondly, my detailed submission, which includes as an annex a draft book on the subject of the epidemiology of ETS in adults, covers in great detail all the questions the SAB has been asked to address. Indeed my analysis of some of the issues is more extensive than has previously been conducted. Since there is not enough time today to get into the detail, I would ask that the SAB pay particular attention to my written comments. Clearly there is very much wrong of a fundamental nature with the EPA draft, and my main message to the SAB today is to take a close look at my written evidence. I would be most happy, following my talk, to sit down with members of the SAB or EPA, to go through the key issues in detail and clarify any points I make, if that would be helpful.

I would like to start my key comments by turning to the issue of how the EPA conducted their meta-analysis. This is relevant to question (iv)

on the SAB's list. It is clear that this meta-analysis has a number of very important weaknesses.

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Meta-analysis

My first comment, "Criteria undefined", is a general one and refers to the unfortunate absence from the draft report of a section, really a materials and methods section, describing precisely how the meta-analysis was conducted. The reader should be told what were the exact criteria that made a study acceptable or unacceptable for inclusion and what were the procedures used to try to collect together all the relevant published and unpublished material. Where a study provided a number of different analyses, the report should define how (and why) particular results were selected for inclusion.

Turning to some of the specific issues, I note that there are a number of studies providing spousal smoking data which were excluded from the meta-analysis. Any revised report should include data from four additional studies - the large New York case-control study, for which a new paper by Janerich et al supplements data in Varela's 1987 thesis; the new data presented by Geoffrey Kabat at the 1990 Toxicology Forum; and the Japanese studies of Shimizu and Sobue. While the Kabat and Sobue data are quite new, there was absolutely no valid reason to omit the Shimizu and particularly the important Varela data from the report.

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The question of the appropriate exposure index to use in the spouse smoking studies is an important one. Most studies compare never smoking women whose husband has ever smoked with those whose husband has never smoked, and the EPA recognise this by applying their meta-analysis

relative risk to the estimated proportion of US never smokers whose spouse has ever smoked. However there are 3 studies where the EPA have, for no good reason, used a different index of exposure. In the Hirayama and Trichopoulos studies they incorrectly used spouses who were current smokers as the exposed group when they should have used spouses who were ever smokers.

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Turning to the next point, which is relevant also to questions (ii) and (viii) put to the SAB, I feel a major weakness of the draft report is that it uses only spouse smoking data. In 1986 this was not unreasonable as data on other exposures were limited at that time. This is not the case today. The data for workplace exposure, as can be seen from my next

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slide, show no indication at all of an association with ETS. Of 11 relative risk estimates, more than half are less than 1, and only a single study, in one sex only, shows even a marginally significant positive association. A similar conclusion is reached when one looks at the data for childhood exposure. Here, based on data for 11 studies,

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there are about the same number of positive and negative associations, and no statistically significant relative risks. Although Janerich reported a significant increase for heavy childhood exposure, the overall evidence is obviously completely null. It certainly causes a clear bias to concentrate in one's meta-analysis on the one index that shows some positive association, spouse smoking, at the expense of other indices that show nothing at all.

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The final point concerning conduct of meta-analysis relates to consideration of the quality of the studies. The draft EPA report only really considers this when it compares and contrasts the Hirayama and Garfinkel prospective studies. Here it comes up with the quite preposterous view that the Hirayama study is a more reliable source of relevant data. The draft report claims that all scientific doubts regarding Hirayama's study have been resolved, but this is just not so. There are a number of recent papers commenting on various strange features of Hirayama's data which have never satisfactorily been explained. Why does the draft report cite none of these papers? It is interesting to compare the EPA's view that the Garfinkel million person study is a poor one with that of the Surgeon-General, who uses it as a major source of data on smoking and health.

The EPA make no attempt whatsoever to consider quality of data from the case-control studies. In my detailed analysis of the evidence I identified eight studies with clear systematic differences between cases and controls in the circumstances under which the data were collected. These differences included failing to match cases and controls on vital status, use of cases and controls from different hospitals, interviewing cases in hospital and some or all controls elsewhere, and using differing proportions of next-of-kin respondents. It is interesting to compare relative risks in the "poor quality" studies with those in the "better quality" studies. As one can see the poor quality studies gave

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significantly higher relative risks. Weighting on study quality in any sensible way would have reduced the meta-analysis RR estimate, as indeed would using all the relevant data, using a consistent exposure index and using data on workplace and childhood exposure.

Sources of bias

Let us turn now to sources of bias, really issue (v) that SAB have

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been asked to consider. My view is that the draft report is totally inadequate here, taking little or no account of sources of bias that clearly do exist and conducting erroneous adjustments for the single source of bias - misclassification of active smoking status - that they try to take seriously.

I have already mentioned bias due to failure to compare like with

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like so I turn to publication bias. The report claims this does not exist, but this seems not to be true as can be seen from comparisons of the number of lung cancers in the studies in the top third and bottom third of the relative risk distribution. The significantly smaller numbers in the studies with the highest relative risk estimates is consistent with failure to publish results from small studies. The EPA should formally estimate bias from this source.

Confounding is a difficult area to deal with properly, but I found the approach of the EPA draft report superficial. It is not apparent from reading the report that some studies do not even adjust for age, assuming falsely that age matching of cases and controls necessarily means that never smoking cases and controls are age matched. Nor does it

point out that about half the studies of spousal smoking include unmarried subjects in the non-exposed group, producing a confounding between marital status and the index of ETS exposure. Also while it may be true that adjusted relative risks do not differ greatly from unadjusted relative risks, it is not pointed out that the studies where adjustments were attempted were principally those which showed no significant relationship anyway. More work is clearly needed in this area.

Misclassification of active smoking

This is a particularly difficult area to discuss in a short time and I would be happy to expand on any points made in detail later. My submission contains a detailed analysis of the subject and I have also provided a commentary on Judson Wells' submission on the same issue.

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My analysis reveals a considerable number of errors in the methodology used by EPA to adjust for this source of bias. There are four points that particularly need to be taken into account when carrying out the adjustment. The first is that, as the epidemiology concerns never smokers, one's interest should be in misclassification as never smokers. The second is that misclassification rates should be estimated as a proportion of ever smokers, not of never smokers. An observation that in one population 5%, say, of self-reported never smokers have ever smoked cannot be applied to another population with a markedly different underlying smoking frequency. The third point is that one should adjust on an individual study basis and should not attempt to carry out a single adjustment on the meta-analysis relative risk estimate. The fourth point

is that one should use parameters relevant to the study in question. These last two points are graphically illustrated in my next slide. Here

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I estimate the magnitude of bias caused by varying levels of misclassification of ever smokers as never smokers in four scenarios, US women, US men, Asian men and Asian women. The estimates of % ever smoked, % ETS exposed, and RR for active smoking are taken as averages from the appropriate ETS studies. One can see from this table that a 2% misclassification would explain the whole reported association of ETS and lung cancer in US and Asian men. It would also explain a very substantial part if not all of the unadjusted association of ETS and lung cancer in US women, where the meta-analysis relative risk is certainly less than 1.20. It would, however, not explain more than a trivial part of the association of ETS and lung cancer reported in Asian women. Here one would need something like a 35% misclassification rate.

Looking at the actual evidence on misclassification rates, a number of points strike me. Firstly, the rate clearly shows large variation between studies, and obviously depends on the circumstances under which the data were collected. Secondly, the evidence that is available to me suggests on average that about 5% of ever smokers report they have never smoked. Since many of these are ex-smokers and long term ex-smokers at that, the extent of bias caused is perhaps more comparable to that caused by 2% of average ever smokers reporting they have never smoked. Thirdly, and absolutely vitally to the whole issue, all the evidence on misclassification is based on data for Western populations. There are strong suspicions from a number of sources that, because of the social stigma against women smoking in Japan, misclassification rates may be far

higher than in the West but we just do not know the true situation. There are no cotinine studies.

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This last point is of major importance to deciding whether or not to carry out meta-analysis based on US data alone, or possibly in conjunction with Western European data, or whether to use all the evidence. My personal view is that it would be sensible not to use the Asian data. Not only is there really no useful misclassification data to use to correct relative risk estimates in Asian studies, but, as EPA themselves argue, the extent of ETS exposure may differ between US and Asian populations. As there are by now a lot of US epidemiological studies and as the objective is to provide estimates of risk to the US population, who clearly differ in many ways from Asian populations, I would stick to the US data. At the very least I would present results calculated in both ways to illustrate the uncertainty involved in the estimation process.

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This leads me onto my final major complaint, that the draft EPA report has not begun to characterize the uncertainties involved in the estimation process. The confidence limits on numbers of deaths and population-attributable risks presented are far too narrow for at least 4 reasons:

(i) They fail to express the fact that estimates vary wildly depending on whether Asian data are or are not used.

(ii) They do not make it clear that over half the US studies have risks estimated by the EPA to be below the lower 95% confidence limit.

(iii) They fail to express the fact that they include a substantial component from deaths in ex-smokers when one has essentially no epidemiological data on ex-smokers to work with and no reason to believe that if ETS does have an effect it is the same as in never smokers.

(iv) They very importantly fail to express the fact that dosimetric based estimates come up with estimates of deaths attributable to ETS orders of magnitude lower than those based on the fragile epidemiological data. If EPA wish to give any sort of real indication of the uncertainty involved they should present estimates calculated in both ways.

The EPA conclude with 95% confidence that at least 1800 deaths per year occurring in US never and ex-smokers are due to ETS. I put it to the SAB that this sort of statement denigrates science. ETS has not yet been convincingly demonstrated to cause lung cancer and even if it does could well be responsible for a number of lung cancer deaths that is two or three orders of magnitude below their lower 95% confidence limit.

META-ANALYSIS CONDUCT

(SAB issue iv)

- Criteria undefined
- Relevant studies omitted
- Inconsistent exposure index used
- Data on workplace and childhood exposure ignored
- Quality of studies inadequately considered

USE CONSISTENT EXPOSURE INDEX

Among women who have never smoked

Compare

1. Husbands who have NEVER smoked
2. Husbands who have EVER smoked

Relevant to Hirayama
Trichopoulos
Garfinkel (case-control)

LUNG CANCER AND ETS EXPOSURE AT WORK

Garfinkel II*	Female	0.88	(0.66 – 1.18)
		0.93	(0.73 – 1.18)
Kabat I	Female	0.68	(0.32 – 1.47)
	Male	3.27	(1.01 – 10.6)
Kabat II	Female	1.00	(0.49 – 2.06)
	Male	0.98	(0.46 – 2.10)
Lee	Female	0.63	(0.17 – 2.33)
	Male	1.61	(0.39 – 6.60)
Shimizu	Female	1.20	(0.44 – 1.37)
Varela**	Both	0.91	(0.80 – 1.04)
Wu	Female	1.30	(0.50 – 3.30)

*Exposure in last 5 years and in last 25 years

**Per 150 person/years smoking in the workplace

LUNG CANCER AND ETS EXPOSURE IN CHILDHOOD

Akiba	Combined	Parents	"No association"
Correa	Combined	Parents	"No sig increase"
Gao	Female	Cohabitant	1.10 (0.70 – 1.70)
Garfinkel II	Female	Any	0.91 (0.74 – 1.12)
Kabat II	Female	Family	1.68 (0.86 – 3.27)
	Male		0.73 (0.34 – 1.59)
Koo	Female	Household	0.55 (0.16 – 1.77)
Pershagen	Female	Parents	1.00 (0.40 – 2.30)
Sobue	Female	Father	0.60 (0.40 – 0.91)
		Mother	1.71 (0.95 – 3.10)
		Other family	1.13 (0.69 – 1.87)
Svensson	Female	Father	0.90 (0.40 – 2.30)
		Mother	3.30 (0.50 – 18.8)
Varela	Combined	Household	1.30 (0.85 – 2.00)
Wu	Female	Parents	0.60 (0.20 – 1.70)

LUNG CANCER RELATIVE RISK FOR SPOUSE SMOKING FEMALES

Studies with obvious failure to compare like with like are highlighted

Inoue		2.55	Koo		1.55	Shimizu		1.08
Humble I	*	2.34	Akiba		1.52	Lee		1.03
Geng		2.16	Hirayama		1.38	Pershagen		1.03
Trichopoulos	*	2.08	Svensson	*	1.26	Sobue		0.94
Correa	*	2.07				Buffler		0.80
Lam I	*	2.01	Garfinkel II		1.23	Kabat II		0.90
Hole		1.89	Wu		1.20	Kabat I		0.79
Brownson	*	1.82	Gao		1.19	Chan		0.75
Lam II	*	1.65	Garfinkel I		1.17	Varela	*	0.75

SOURCES OF BIAS

(SAB issue v)

- Failure to compare like with like
- Publication bias
- Confounding
- Misclassification of active smoking status

SPOUSE SMOKING AND LUNG CANCER
EVIDENCE OF PUBLICATION BIAS
IN STUDIES ON FEMALES

8 Studies with highest relative risk estimates (>1.80)

Numbers of lung cancers 6, 19, 20, 22, 22, 54, 60, 77
mean 35 median 22

8 studies with lowest relative risk estimates (<1.05)

Numbers of lung cancers 24, 32, 41, 53, 70, 84, 120, 144
mean 71 median 61.5
($p<0.05$)

MISCLASSIFICATION OF ACTIVE SMOKING STATUS

- Misclassification as NEVER smokers
- Misclassification as a proportion of EVER smokers
- Adjust study by study
- Use parameters relevant to study

BIAS FROM MISCLASSIFICATION IN FOUR SCENARIOS

Scenario	% Ever Smoked	% ETS Exposed	RR Smoking	Misclass Rate	Bias *
US women	49.0	54.3	6.73	1%	1.06
				2%	1.12
				5%	1.35
				10%	2.02
US men	77.1	38.7	11.83	1%	1.52
				2%	2.38
Asian women	24.5	56.9	2.99	10%	1.07
				25%	1.26
				40%	1.73
				50%	2.82
Asian men	80.8	6.6	3.48	1%	1.20
				2%	1.42
				5%	2.36

* Assuming concordance ratio of 3.0

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INCLUDE ASIAN EVIDENCE?

(SAB issue iii)

Highly dubious because:

- Extent of exposure may differ
- No Asian misclassification data
- Objective to provide US estimate

CHARACTERIZE UNCERTAINTIES

(SAB issue vi)

- US vs All
- Ex-smokers
- Dosimetric vs Epidemiological